

242 DIABETES MELLITUS

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OVERVIEW

Diabetes mellitus is a chronic disorder characterized by impaired metabolism of glucose and other energy-yielding fuels, as well as the late development of vascular (involving small and large blood vessels) and neuropathic complications. Diabetes mellitus consists of a group of disorders involving distinct pathogenic mechanisms in which hyperglycemia is the common denominator. Regardless of the cause, the disease is associated with a common hormonal defect, namely, insulin deficiency, which may be total, partial, or relative when viewed in the context of coexisting insulin resistance. Lack of insulin plays a primary role in the metabolic derangements linked to diabetes, and hyperglycemia in turn plays a key role in the complications of the disease.

In the United States the number of diagnosed cases of diabetes mellitus has substantially increased in the last half of the 20th century. Diabetes mellitus is the fourth most common reason for patient contact with a physician, accounts for nearly 15% of health care costs in the United States, and is a major cause of premature disability and mortality. It is the leading cause of blindness among working-age people, of end-stage renal disease (ESRD), and of non-traumatic limb amputations. It increases the risk of cardiac, cerebral, and peripheral vascular disease two- to seven-fold and is a major factor contributing to neonatal morbidity and mortality. On the bright side, recent data indicate that most, if not all of the debilitating complications of the disease can be prevented or delayed by prospective treatment of hyperglycemia and other cardiovascular risk factors.

CLASSIFICATION

The newly revised classification of diabetes mellitus is summarized in Table 242-1. Clinical diabetes may be divided into four general subclasses, including (1) type 1 (caused by beta cell destruction and characterized by absolute insulin deficiency), (2) type 2 (characterized by insulin resistance and relative insulin defi-

ciency), (3) other specific types of diabetes (associated with various identifiable clinical conditions or syndromes), and (4) gestational diabetes mellitus. In addition to these clinical categories, two conditions—impaired glucose tolerance and impaired fasting glucose—refer to a metabolic state intermediate between normal glucose homeostasis and overt diabetes. These conditions significantly increase the later risk of diabetes mellitus and may in some instances be part of its natural history. It should be noted that patients with any form of diabetes may require insulin treatment at some point. For this reason the previously used terms insulin-dependent diabetes (for type 1 diabetes mellitus) and non-insulin-dependent diabetes (for type 2) have been eliminated.

TYPE 1 DIABETES MELLITUS. Patients with this disorder have little or no insulin secretory capacity and depend on exogenous insulin to prevent metabolic decompensation (e.g., ketoacidosis) and death. Commonly but not always, diabetes appears abruptly (i.e., over days or weeks) in previously healthy non-obese children or young adults; in older age groups it may have a more gradual onset. At the time of initial evaluation the typical patient often appears ill, has marked symptoms (e.g., polyuria, polydipsia, polyphagia, and weight loss), and may demonstrate ketoacidosis. Type 1 diabetes is believed to have a long asymptomatic pre-clinical stage often lasting years, during which pancreatic beta cells are gradually destroyed by an autoimmune attack that is influenced by HLA and other genetic factors, as well as the environment (Fig. 242-1). In some, an acute illness may speed the transition from the pre-clinical to the clinical stage. Initially, insulin therapy is essential to restore metabolism toward normal. However, a so-called honeymoon period may follow and last weeks or months, during which time smaller doses of insulin are required because of partial recovery of beta cell function and reversal of insulin resistance caused by acute illness. Thereafter, insulin secretory capacity is gradually lost (over several years). That type 1 diabetes is an autoimmune disease is supported by its association with specific immune response (HLA) genes and the presence of antibodies to islet cells and their constituents. This syndrome accounts for less than 10% of diabetes in the United States.

TYPE 2 DIABETES MELLITUS. Type 2, by far the most common form of the disease, is found in over 90% of the diabetic patient population. These patients retain a significant level of endogenous insulin secretory capacity. However, insulin levels are low relative to the magnitude of insulin resistance and ambient glucose levels. Type 2 patients are not dependent on insulin for immediate survival and ketosis rarely develops, except under conditions of great physical stress. Nevertheless, these patients may require insulin therapy to control hyperglycemia. Type 2 diabetes typically appears after the age of 40 years, has a high rate of genetic penetrance unrelated to HLA genes, and is associated with obesity. The clinical features of type 2 diabetes are much more insidious. The classic symptoms of diabetes may be mild (fatigue, weakness, dizziness, blurred vision, or other non-specific complaints may dominate the picture) or may be tolerated for many years before the patient seeks medical attention. Moreover, if the level of hyperglycemia is insufficient to produce symptoms, the disease may become evident only after complications develop.

OTHER SPECIFIC TYPES OF DIABETES. This category encompasses a variety of diabetic syndromes attributed to a specific disease, drug, or condition (see Table 242-1). Genetic research has provided new insights into the pathogenesis of maturity-onset diabetes of the young (MODY), which was formerly included as a form of type 2 diabetes. MODY encompasses several genetic defects of beta cell function, among which mutations at several genetic loci on different chromosomes have been identified. The most common forms—MODY type 3—is associated with a mutation for a transcription factor encoded on chromosome 12 named hepatocyte nuclear factor 1 α (HNF-1 α) and -MODY type 2 is associated with mutations of the glucokinase gene (on chromosome 7). Mutations of the HNF-4 α gene (on chromosome 20) are responsible for type 1 of MODY. Each of these conditions is inherited in an autosomal dominant pattern. Two new rare forms of MODY are associated with mutations of the HNF-1 β (on chromosome 17) and an insulin gene transcription factor termed PDX-1 or IDX-1 (on chromosome 13).

It should be emphasized that severe illness (e.g., burns, trauma, sepsis) may also provoke stress hyperglycemia as a result of hypersecretion of insulin antagonistic hormones. Although some of

Table 242-1 ■ CLASSIFICATION OF DIABETES

Clinical Diabetes

- I. Type I diabetes, formerly called insulin-dependent diabetes mellitus (IDDM) or "juvenile-onset diabetes"
 - A. Immune mediated
 - B. Idiopathic
- II. Type II diabetes, formerly called non-insulin-dependent diabetes (NIDDM) or "adult-onset diabetes"
- III. Other specific types
 - A. Genetic defects of β -cell function (e.g., maturity-onset diabetes of the young [MODY] types 1-3 and point mutations in mitochondrial DNA)
 - B. Genetic defects in insulin action
 - C. Disease of the exocrine pancreas (e.g., pancreatitis, trauma, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy)
 - D. Endocrinopathies (e.g., acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma, glucagonoma, somatostatinoma, aldosteronoma)
 - E. Drug or chemical induced (e.g., glucocorticosteroids, thiazides, diazoxide, pentamidine, vacor, thyroid hormone, phenytoin [Dilantin], β -agonists, oral contraceptives)
 - F. Infections (e.g., congenital rubella, cytomegalovirus)
 - G. Uncommon forms of immune-mediated diabetes (e.g., "stiff-man" syndrome, anti-insulin receptor antibodies)
 - H. Other genetic syndromes (e.g., Down, Klinefelter's, Turner's syndrome, Huntington's disease, myotonic dystrophy, lipodystrophy, axtia-telangiectasia)
- IV. Gestational diabetes mellitus
 - Risk categories
 - I. Impaired fasting glucose
 - II. Impaired glucose tolerance